REMARKS

Applicant hereby submits claims 22-30, to replace claims 1, 5-12, and 21 previously considered by the Examiner. A new claim 31, has been added.

We hereby provide a detailed account for the support of the amendments to the claims as well as our arguments in response to the Examiner's objections.

With respect to the limitation of the claims to the treatment and prevention of systemic inflammatory response syndrome (SIRS) we refer to the review article of Nyström entitled "The Systemic Inflammatory Response Syndrome: definitions and Aetiology," (enclosed), which deals with the definitions and etiology of SIRS. The introduction of this article cites as reference 1 the reference of Bone et al., a reference that is also cited in paragraph 4 of the published application.

> *"The introduction of the term 'systemic inflammatory response syndrome' (SIRS) by the* American *College of Chest Physicians and Society of Critical Care Medicine (ACCP/SCCM) consensus conference[1] recognised the important role that endogenous mediators of systemic inflammation play in 'sepsis', which was no longer regarded as being caused by microbial pathogenicity factors alone."*

Table III on page 3 of the Nyström article, presents the definition of SIRS and indicates well that sepsis is a SIRS as it has two of the conditions mentioned in the definition of SIRS.

> *"SIRS : the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: temperature > 38°C or < 36°C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or PaCO2 < 32 torr (< 4.3 kPa); WBC > 12,000 cells/mm3, < 4000 cells/mm3 or > 10% immature (band) forms"*

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> "Sepsis : the systemic *response* to infection; this response is manifested by two or more of the SIRS criteria as a result of infection"

Consequently, it is respectfully submitted that sepsis is a condition resorting under the general term SIRS and the treatment and/or prevention of sepsis can thus be seen as a particular embodiment of the claims as presently amended.

1. Amendments

With reference to the listing of claims, new claims 22 to 30 correspond to the subject matter previously claimed in claims 5-12 and 21.

Present claim 22, corresponds to previous claim 1, but has been amended as follows:

- the claim now refers to SIRS (systemic inflammatory response syndrome) and no longer cites different diseases.
- The claim now refers to 'a monoclonal antibody a monoclonal antibody against Factor VIII or an antigen binding fragment of said monoclonal antibody
- the limitation of previous claim 7, which specified binding to the C1 domain of factor VIII has been introduced.

Support in the description for the amendments in claim 22 is found in

- paragraph 14:

> "*The present invention first provides a method for preventing and/or treating a systemic inflammatory response syndrome (SIRS) in mammals by (i.e. the said method comprising or, preferably, consisting essentially of) partially inhibiting the formation of thrombin, for instance by administering a partial inhibitor of factor VIII to the mammal in need thereof.*

- paragraph 14:

> *"In the various above-mentioned aspects of the present invention, the partial inhibitor of factor VIII may be a ligand, preferably other than a polyclonal antibody, more preferably* ***a monoclonal antibody or antigen-binding fragment thereof****...*(emphasis added)

- paragraph 38:

> *"The present invention also provides* ***fragments of any of the above monoclonal antibodies*** *[...]. More particularly, these* ***monoclonal antibodies and fragments may target a domain of factor VIII, in particular the C1 domain of factor VIII****"*(emphasis added)

Previous claims 6, 8 and 10, 12 and 21 have been reordered into present claims 25, 23-24, 26, 28 and 29, respectively.

Claim 27 (Previous claim 5) has been amended to refer only to the monoclonal antibody obtainable from the deposited cell line.

Claim 28 corresponds to previous claim 11, but has been limited to certain types of fragments, particularly considered in the context of the present invention. Moreover the claim has been limited to fragments obtainable from the deposited cell line.

Support in the description for claim 28 can be found in paragraph 38:

> *"The present invention also* ***provides fragments of any of the above monoclonal antibodies such as Fab, Fab', F(ab').sub.2, scFv,*** *[...].*

New claim 30 relates to a specific embodiment of the invention, whereby the antibodies have at least 80% sequence identity with the antibodies obtainable from the deposited cell line. Support for new claim 30 can be found in paragraph 31 (of the published application):

> *"Where the said ligands include amino-acid sequences, then, homology should include having at least 80%, more*

> *preferably 90% and most preferably 95% amino acid sequence identity with the relevant ligand".*

and especially in paragraph 48:

> *"Most preferably the said monoclonal antibody is a human monoclonal antibody, or a fragment or* ***a homologue thereof,*** *obtainable from the cell line KRIX 1 deposited with the Belgian Co-ordinated Collections of Micro-organisms under accession number LMBP 5089CB.* ***The degree of homology with the said monoclonal antibody is preferably at least 80%,*** *more preferably 90% and most preferably 95%, and the homology is preferably particularly in respect to the complementarity determining regions of the antibody"*

2. Objections presented in the Office Action

a) Objection under 35 U.S.C.112, second paragraph (items 6-7 of the Office Action)

It is respectfully submitted that the removal of the reference to "having a reactivity substantially identical to" in the amended claims filed herewith, should render this objection moot

Moreover, the objection to previous claim 8 has been overcome by inserting the subject matter of claim 8 in two separate claims, as has been done in present claims 23 and 24.

b) Objection under 35 U.S.C.112, first paragraph (items 9 of the Office Action)

The KRIX-1 cell line has been deposited by one of the inventors (Dr. M. Jacquemin) in a recognized depository institution resorting under the Budapest Treaty as mentioned in the specification of the published application on page 4, paragraph 39:

> *"The cell line named KRIX 1 producing monoclonal antibodies as used in the present invention was deposited with the BCCM.TM./LMBP (Belgian Co-ordinated ollections of Microorganisms/Plasmid Collection*

Laboratorium voor Moleculaire Biologie, University of Ghent K. L. Ledeganckstraat 35, B-9000 Ghent, BE under accession number LMBP 5089CB on Jul. 1, 1999".

The deposit is thus present in a public depository and in accordance with rule 9.1 of the Budapest Treaty. A copy of the receipt provided to Applicant by the BCCM indicating that this deposit was received under the Budapest Treaty, as well as the requested statement with regard to its availability are attached. We enclose a declaration of the inventor certifying the availability of the deposit. Given this statement and Applicant's Declaration, Applicant submits that this part of the rejection should therefore be withdrawn.

With regard to the further objections made with regard to the enablement of the claims, it is respectfully submitted that the amended claims as filed herewith now refer to inhibitory antibodies and fragments with defined binding properties (against the C1 domain of FVIII).

We submit that the specification clearly provides enablement for a method for preventing and/or treating SIRS by administrating an antibody to the C1 domain of FVIII or an antigen-binding fragment thereof, and that thus the description is commensurate in scope with the broadest claim presently submitted. Indeed the Examiner has acknowledged the enablement of the description for 'anti-FVIII C1 domain' antibodies and more particularly for the antibody produced by the deposited KRIX-1 cell-line. Thus, this amendment should render the Examiner's objections made in the three last paragraphs of page 4 of the office action moot.

The Examiner has moreover brought the argument that *in vitro* studies do not correlate well with in vivo clinical trial results in patients and thus questions the reliability of the data obtained *in vitro* with the antibodies of the present invention as enabling disclosure.

Without acquiescence of the Examiner's objection, we hereby submit a declaration from one of the inventors, dr. Jean-Marie Saint-Rémy, which provide additional *in vivo* data of an anti- FVIII C1 domain antibody, which is a partial inhibitor of FVIII in mice, and demonstrate that it can be administered in elevated dosages without the side-effects typically observed for complete FVIII inhibitors and that it is capable of preventing LPS-induced shock in a well established mouse model. Thus, the in vitro thrombin formation demonstrated for anti-FVIII C1 domain antibodies

can be considered to be representative for an *in vivo* partial inhibition and, more importantly, for a therapeutic application of these antibodies in the treatment and prevention of SIRS.

The examiner has indicated in the Office action on page 5, third paragraph that there may be a concern for bleeding as a result of the inhibition of FVIII. It is respectfully submitted that this is exactly one of the major features of the present invention as specified in the claims, i.e. the antibodies are only partially inhibitory so that, regardless of the concentration being used, a residual activity of FVIII is maintained. A consequence of this feature (also referred to as 'plateau effect' is that the there is always a sufficiently high level of FVIII to avoid the bleeding disorders which would occur with complete FVIII inhibition.

The Examiner has moreover referred to a publication by Taylor et al. (1997), to demonstrate the lack of correlation sometimes observed between *in vivo* data in animals and what occurs in humans. The article of Taylor deals with a combination of C4bBP and living E. coli bacteria as a model for human diffuse intravascular coagulation, thrombotic thrombocytopenic purpura, and hemolytic uremic synsufficient drome. This syndrome induced by the combination of C4bBP and E coli and, the author states in the article, it has "**elements that are similar** to those observed in [diffuse intravascular coagulation, thrombotic thrombocytopenic purpura, and hemolytic uremic synsufficient drome]" (page 4078, left column, line (emphasis added)). Further on in the article, it is also mentioned that the platelets "**at least in part** mediate the tissue damage associated with these syndromes]" (page 4078, left column, line 17-19 (emphasis added). (emphasis added).

Thus, Taylor himself indicates that the C4bBP + *E. coli* treatment only partially_mimics the mentioned disorders and based thereon concludes that a treatment at the level of platelet aggregation will be only a partial solution for curing these disorders.

This notion of the fact that a non-perfect model was used for the disorders studied, is also mentioned at the end of the discussion of the article. From this it can be deduced that Taylor ascribes the differences in the pathophysiology between model and disease not to the differences between baboon and man but rather to the differences between the model and the disorders themselves. We submit that the Taylor article at most suggests that it is difficult to extrapolate from a model which in his opinion only reflects some aspects of the actual disease as observed in

humans, and it is sumbitted that the article gives no warnings of extrapolating baboon results to humans.

In this context it is noteworthy that the C4bBP protein, referred to in the Taylor et al. publication is reported to lead to inhibition of Protein C. It is precisely this inhibition which is prevented in the present invention, as partial inhibition of Factor VIII makes it possible to preserve Protein C activity. This further stresses major differences between the cited article and the present invention.

With respect to the enablement rejection, the examiner is directed to MPEP § 2164.02 setting for the standard for evaluating the correlation between the animal model and the method of use. "....if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating unless the examiner has evidence the model does not correlate". We moreover respectfully submit that the animal model used in the *in vivo* experiments described in the application or those presented in the declaration submitted herewith is a well-established model for sepsis.

It is respectfully submitted that the objections raised under 35 U.S.C 112, first paragraph under item 10 of the Office Action should also be rendered moot by the amendments to the claims, whereby the scope has been restricted to the use of monoclonal anti-FVIII C1 domain antibodies, and the in vivo data demonstrating the fact that indeed these monoclonal anti-FVIII C1 domain antibodies have therapeutic application in the prevention and/or treatment of sepsis.

The limitation of the claims relating to the use of a partial inhibitor of FVIII to the antibodies which bind to the C1 domain of FVIII provides a clear functional description of the antibodies of the invention. This specification provides clear written description on how such antibodies can be obtained. As antibodies are generally defined and identified by their binding properties and not by their actual molecular structure, it is submitted that the determination of these specific binding properties corresponding to the genus and how antibodies falling within this genus can be selected for as provided in the specification provides sufficient written description to demonstrate that the applicant was in possession of the genus.

In view of the amendments and remarks, the application is now in condition for allowance and favorable consideration is requested.

Respectfully submitted,

Peter J. Shakula
Registration No. 40,808

BARNES & THORNBURG
One North Wacker Drive
Suite 4400
Chicago, IL 60606-2809
(312) 214-4813

Dated: October 21, 2004

BELGIAN COORDINATED COLLECTIONS OF MICROORGANISMS - BCCM™ LMBP-COLLECTION

Page 1 of Form BCCM™/LMBP/BP/4/99-14 Receipt in the case of an original deposit

Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure

Receipt in the case of an original deposit issued pursuant to Rule 7.1 by the International Depositary Authority BCCM™/LMBP identified at the bottom of next page

International **Form BCCM™/LMBP/BP/4/99-14**

To : **Name of the depositor :** JACQUEMIN MARC

Address : Center for Molecular and Vascular Biology
Onderwijs & Navorsing
Herestraat 49
3000 Leuven

I. **Identification of the microorganism:**

I.1 **Identification reference given by the depositor:**

KRIX 1

I.2 **Accession number given by the International Depositary Authority:**

LMBP 5089CB

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02447005.6

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Page 1 of Form BCCM™/LMBP/BP/9/99-14 Viability statement

Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure

Viability statement issued pursuant to Rule 10.2 by the International Depositary Authority BCCM™/LMBP identified on the following page

International **Form BCCM™/LMBP/BP/9/99-14**

To : **Party to whom the viability statement is issued:**

Name : JACQUEMIN MARC

Address : Center for Molecular and Vascular Biology
Onderwijs & Navorsing
Herestraat 49
3000 Leuven

I. **Depositor:**

I.1 Name : JACQUEMIN MARC

I.2 Address : Center for Molecular and Vascular Biology
Onderwijs & Navorsing
Herestraat 49
3000 Leuven

II. **Identification of the microorganism:**

II.1 Accession number given by the International Depositary Authority:

LMBP 6089CB

II.2 Date of the original deposit for where a new deposit or a transfer has been made, the most recent relevant date) : July 1, 1999

III. **Viability statement.**

The viability of the microorganism identified under II above was tested on

: July 9, 1999

(Give date. In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test).

On that date, the said microorganism was: (mark the applicable box with a cross)

☒ viable

☐ no longer viable

BELGIAN COORDINATED COLLECTIONS OF MICROORGANISMS

STATEMENT

The Kitx-1 cell line has been deposited with the Belgian Coordinated collections of Microorganisms (BCCM) on July 1st, 1999 and bears the accession number LMBP 5089CB. Applicants acknowledge their responsibility to replace this strain should it lose viability before the end of the term of a patent issued hereon, and their responsibility to notify the BCCM of the issuance of such a patent, at which time the deposit will be made available to the public. Prior to that time the deposit will be made available to the Commissioner of Patents under terms of CFR §1.14 and 35 USC §112.

Dr Marc Jacquemin

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